UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/973,284	10/09/2001	Joy M. Campbell	P05273US0	5785

22885 7590 12/19/2003

MCKEE, VOORHEES & SEASE, P.L.C.
801 GRAND AVENUE
SUITE 3200
DES MOINES, IA 50309-2721

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/973,284	CAMPBELL ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *9-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/15/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/15/03 has been entered.

2. Claims 1-23 are pending.

3. Claims 9-15 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-8 and 16-23 are under examination as they read on a method of treating an animal suffering from an immune dysfunction disease state associated with altered levels of IgG.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1- 8 and 16-23 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating an animal suffering from chronic fatigue syndrome which associated with altered levels of IgG comprising administering orally to said animal immunoglobulin derived from blood, egg, milk, recombinant immunoglobulin expressed in a plant and recombinant immunoglobulin expressed in a bacteria does not reasonably provide enablement for a method for treating an animal suffering from any **chronic immune dysfunction disease** state associated with altered levels IgG comprising administering to said animal an immunomodulating amount of immunoglobulin from an animal source in claims 1 and 16. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims essentially for the same reasons set forth in the previous Office Action, mailed 9/10/02.

While Applicant asserts that the specification is enabling and the amended claims to show that immune dysfunction disease states are those which are characterized by chronic immune stimulation. Further, applicant asserts that the specification teaches that the does and schedules of the immunoglobulin will vary depending on the age, health, sex, size and the weight of the patient rather than administration. Applicant argues that these parameters can be determined for each system by well-established procedures and analysis. Finally, Applicant argues that chronic fatigue syndrome has been shown to resemble other disorders such as multiple sclerosis and lupus.

However, the specification does not adequately teach how to effectively treat any chronic immune dysfunction disease state associated with altered levels of IgG or reach any therapeutic endpoint in animal including humans by administering an animal source imunoglobulin. The specification does not teach how to extrapolate data obtained from the effect of oral administration of plasma protein on antibody responses to primary and secondary rotavirus vaccination in pigs to the development of effective human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the immunoglobulin exemplified in the specification on any chronic immune dysfuction, encompassed by the claims. Further, while the symptoms of chronic fatigue syndrome, multiple sclerosis and systemic lupus erythematosus may look similar. Chronic fatigue syndrome is characterized by debilitating fatigue (experienced as exhaustion an extremely poor stamina), neurological problems, and a variety of flu-like symptoms, multiple sclerosis is an inflammatory demyelinating condition while lupus is any of various chronic skin conditions characterized by ulcerative lesions that spread over the body. Therefore, it is not clear that the skilled artisan could predict the efficacy of the immunoblobulin exemplified in the specification on any of the chronic immune dysfunction disease state.

In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the methods as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for in vivo human use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed methods with a reasonable expectation of success.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

8. Claims 1-4, 8, 16-19 and 23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lloyd *et al* (Am J Med. 1990, 89:561-568), as is evidenced by INTRAGAM® Data Sheet, in view of EP 0064 210 A1 (IDS Ref. No. 7) or in view of U.S. Patent No. 5,871,731.

The Lloyd *et al* teach a method of treating patients suffering from chronic fatigue syndrome that is characterized by IgG subclass deficiency (page 561, right column 3rd paragraph in particular) comprising administering to the patients an immunomodulating amount of immunoglobulin (INTRAGAM®) from an animal source (page 562, under Drug Formulation in particular). Lloyd *et al* further teach that immunoglobulin is administered by continuous infusion in dosage of 2g (IgG)/kg or placebo (10% w/v maltose) (page 562, under Drug Formulation in particular). Immunoglobulin in placebo is considered as composition. Further, as is evidenced by INTRAGAM® Data Sheet that INTRAGAM® is made by a cold ethanol fractionation of large pools of human plasma obtained from voluntary blood donors (page 1, paragraph 2 in particular).

The claimed invention differs from the reference teachings only by the recitation that the immunomodulating amount of immunoglobulin is administered orally in claim, immunoglobulin from an animal source is blood and fractions thereof in claim 2, egg and fractions thereof in claims 3 and 18 and milk and fractions thereof in claims 4 and 19.

The `210 publication teaches oral pharmaceutical composition containing immune globulin for therapeutic. The `210 publication further teaches that oral administration of IG has advantages over parenteral administration wherein the primary advantage is the avoidance of injection, either intramuscularly or intravenously and the discomforts. The `210 publication further teaches that an oral IG composition provides ease of administration and avoids the pain associated with parenteral administration. Finally, the `210 publication teaches that larger doses of IG can be administered orally than parenterally (see the entire document, and page 4 lines 5-14 in particular).

The `731 patent teaches that oral administration of immunoglobulins from plasma, colostral milk, milk, eggs or cell cultures in a method of treating chronic pain syndrom. The `731 patent further teaches that the immunoglobulins can be prepared by known techniques from plasma, for example from eggs or from milk. Furthermore, the isolation of immunoglobulins from milk of immunized cows or from eggs from immunized hens is used to immunize pregnant women or mother animals against bacterial pathogens (column 3, lines 31-36 in particular). The `731 patent further teaches that the production of the immunoglobulins from plasma is relatively complicated and therefore very expensive, the immunoglobulins are preferably isolated from milk (see the entire document and column 2, lines 61-67 and column 3, lines 1-2 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made administer the immunoglobulin taught by the Lloyd *et al* orally as taught by the `210 publication or the `731 patent and further to substitute the immunoglobulin from egg or from milk taught by the `731 patent with the immunoglobulin from blood taught by Lloyd et al in a method of treating an animal suffering from chronic fatigue syndrome taught by Lloyd *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because oral IG composition provides ease of administration and avoids the pain associated with parenteral administration. Further, larger doses of IG can be administered orally than parenterally as taught by `210 publication. Further, producing immunoglobulin from milk is easy and inexpensive and producing immunoglobulins from milk of immunized cows or from eggs from immunized hens is used to immunize pregnant women or mother animals against bacterial pathogens as taught by the `731 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

While Applicant argues that there is no suggestion in the cited references that they by combined in the manner proposed by the Examiner. Applicant further argues that the `731 patent is not only unconcerned with CFS and intravenous administration of an immunoglobulin but teaches the immunoglobulins are most preferably from colostral milk. Applicant further argues that Lloyd et al teach a method of treating CFS with immunoglobulins made from human plasma via intravenous administration. Further, Lloyd et al, do not suggest or teach using an immunoglobulin derived from milk or egg. In addition, the `731 patent teaches treatment of chronic pain syndrom, not chronic fatigue syndrome where the immunoglobulin is isolated from milk. Applicant further argues that the current invention differs from the `731 because there is no need for preimmunization. Applicant arrives to the conclusion that one skilled in the art would not likely use such a reference alone or in combination with another reference in an attempt to solve such a problem. Finally applicant argues that the current invention over come what the `731 patent views as an insuperable barrier.

Contrary to the applicant assertion, Lloyd et al, teaches a method of treating CFS comprising administering an immunoglobulin from animal source. Further, the `731 patent teaches the oral administration of immunoglobulins from, plasma, colostral milk, milk, eggs or cell cultures in a method of treating chronic pain syndrome. Therefore, the `731 patent teaches both colostral milk as will as milk.

The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991) (discussed below). Although Ex parte Levengood, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) states that obviousness cannot be established by combining references "without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done " (emphasis added), reading the quotation in context it is clear that while there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention.

9. Claims 5-6 and 20-21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lloyd *et al* (Am J Med. 1990, 89:561-568), as is evidenced by INTRAGAM® Data Sheet, in view of EP 0064 210 A1 as applied to claims 1-4, 8, 16-19 and 23 or in view of U.S. Patent No. 5,871,731 above, and further in view of WO 96/21012 (1996).

The teachings of Lloyd *et al* reference, the `731 patent and the `210 publication have been discussed, supra.

The claimed invention further differs from the reference teachings only by the recitation that the animal immunoglobulin is recombinant in claims 5 and 20 wherein the recombinant is expressed in a plant in claims 6 and 21.

The `012 publication teaches the production of large amounts immunoglobulins in plants with great efficiency and economical feasibility (see page 5 lines 31-35 in particular) using recombinant vector (see page 54 lines 34-35 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunoglobulin that is expressed in a plant using recombinant vector taught by the `102 publication with the immunoglobulin from blood in a method of treating an animal suffering from chronic fatigue syndrome taught by Lloyd *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because immunoglobulins expressed in plants have great efficiency and economical feasibility as taught by `012 publication.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

While Applicant argues that there is not suggestion in the cited references that they be combined in the manner proposed by the Examiner. Applicant further argue that the is no motivation found in the `012 publication because the `012 publication discloses a method for assembling secretory immunoglobulins, which do not stimulate the complement system by functions by inhibiting microorganisms for binding to the epithelium.

Contrary to applicant assertion, the `012 publication teaches the production of large amounts immunoglobulins in plants with great efficiency and economical feasibility using recombinant vector. Examiner notes that the instant claims and specification do not provide a mechanism of action on how the recombinant immunoglobulin expressed in the plants produced or function. Further, the specification does not disclose whether the plant secrets the immunoglobulin or does not secret the immunoglobulin.

Further, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144.

10. Claims 5, 7, 20 and 22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lloyd *et al* (Am J Med. 1990, 89:561-568), as is evidenced by INTRAGAM® Data Sheet, in view of EP 0064 210 A1 or in view of U.S. Patent No. 5,871,731 as applied to claims 1-4, 8, 16-19 and 23 above, and further in view of U.S. Patent No. 5,348,867 (1994).

The teachings of Lloyd *et al* reference, the `731 patent and the `210 publication have been discussed, supra.

The claimed invention further differs from the reference teachings only by the recitation that the animal immunoglobulin is recombinant in claims 5 and 20 wherein the recombinant is expressed in bacteria in claims 7 and 22.

The `867 patent teaches recombinant immunoglobulins from bacteria. The `867 patent further teaches that the variety of recombinant immunoglobulins from bacteria is greater than the number of antibody molecules that can be generated by the mammalian cell (column 2, line 68 and column 3, lines 1-12 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the recombinant immunoglobulins that is expressed in a bacteria taught by the `867 publication with the immunoglobulin from blood taught by Lloyd *et al* and administering the immunoglobulin orally as taught by the `731 patent or `012 publication in a method of treating an animal suffering from chronic fatigue syndrome taught by Lloyd *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the variety of recombinant immunoglobulins from bacteria is greater than the number of antibody molecules that can be generated by the mammalian cell as taught by `867 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant argues that there is no suggestion in the cited references that they be combined in the manner proposed by the Examiner. Applicant further argues that the `867 merely teaches a recombinant DNA vector that promotes transport of a periplamic or other protein to external face of the outer membrane of a gram negative bacterial cells in the absence of any specific export components which is distinguishable from Applicant's claimed invention wherein the immunoglobulin is purified from "transgenic" bacteria.

Examiner does not see the distinction between applicant's usage of immunoglobulin purified from "transgenic" bacteria and the recombinant immunoglobulin expressed in the bacteria taught

by the `871 patent. Furthermore, claims 7 and 22 recite a recombinant immunoglobulin expressed in bacteria.

Further, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-8 and 16-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 33-39 and 44 of copending Application No. 09/973,283. Although the conflicting claims are not identical, they are not patentably distinct from each other because treating a chronic immune dysfunction disease/modulating the immune response of an animal language reads on one another specially both method are associated with altered levels of IgG and require the oral administration of the same immunoglobulin from an animal source, wherein the animal source is blood and fractions thereof, egg and fractions thereof, milk and fractions thereof, or recombinant immunoglobulin expressed in plants or bacteria.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. No claim allowed

14. This is a RCE of applicant's earlier Application No. 09/973,284. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
December 11, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600